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Local weather, flooding history and childhood diarrhoea caused by the parasite *Cryptosporidium* spp.: A systematic review and meta-analysis

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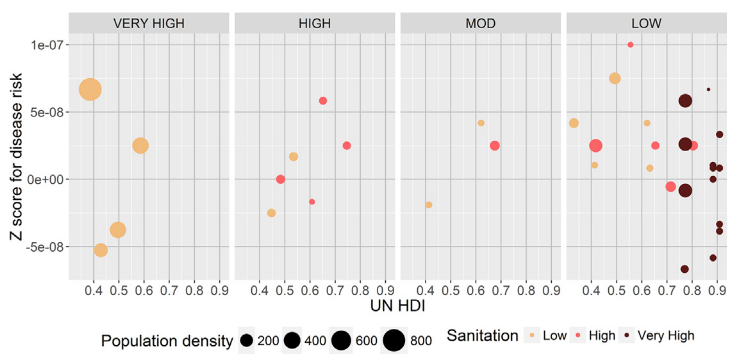
HIGHLIGHTS

- Globally, cryptosporidiosis in children is linked to local rainfall and population density.
- Historical flooding is related to childhood cryptosporidiosis.
- We need a cross-sectoral response to water-related health threats expected environmental change.

GRAPHICAL ABSTRACT



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ABSTRACT

Scientists have long predicted the impacts of climate-related infectious disease emergence. Yet, the combined effect of local socioeconomic and demographic factors and weather variation on child health is poorly understood. With a focus on childhood diarrhoea caused by the parasite *Cryptosporidium* spp., - an infection easily controlled by public health interventions but also strongly linked to environmental conditions through waterborne spread, we systematically review and empirically model the effects of local weather and flooding history, after controlling for seasonality, publication bias, access to improved sanitation, health resources and population density at a global scale. We examined 1588 papers on childhood cryptosporidiosis and identified 36 studies representing a range of geographic locations and climatic, environmental and socio-economic conditions. Local rainfall and population density were related with cryptosporidiosis across latitudes as shown by mixed effects, spatio-temporal models for equatorial, subtropical and temperate climates. In equatorial (0–20°) latitudes, the previous month's rainfall and population density were inversely related with childhood cryptosporidiosis with a significant random effect for flooding history. In tropical-subtropical (20–35°) latitudes, rainfall in December was inversely related with cryptosporidiosis, compared to rainfall in April (the wet season). In temperate latitudes (>35°), there was a significant negative association of reported disease with population density. This global empirical analysis indicates differential spatio-temporal patterns of childhood cryptosporidiosis in low, mid and high latitude regions. Models that couple weather conditions with demographic factors are needed to assess disease distributional shifts and risks due to environmental change. These results may provide impetus to develop environment-focused public health policies to manage disease risks associated with climate change for future generations.

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1. Introduction

The frequency of floods and population growth are expected to increase in many low-latitude countries (Hirabayashi et al., 2013). Here, waterborne diarrhoea is a leading cause of morbidity and mortality among children (Walker et al., 2013; Lopez et al., 2006). Substantial gains in public health and infectious disease control in the past century have resulted in diarrhoeal mortality declining at 4% per year (Liu et al., 2012), with an estimated 74% of diarrhoea related deaths in children younger than five years clustered in a limited number of countries (Walker et al., 2013). In contrast, trajectories of diarrhoeal disease incidence are decreasing more slowly (Walker et al., 2012) and regional patterns are not as distinct (Walker et al., 2013). Global insights into region-specific environmental and social risk factors may inform targeted interventions to further accelerate the reduction in diarrhoeal incidence in the context of projected environmental change.

Cryptosporidiosis is a major cause of parasitic diarrhoea in children. In the three year prospective Global Enteric Multicenter Study of childhood diarrhoea, the parasite *Cryptosporidium* was the second leading cause (5–15%) of moderate-to-severe diarrhoea in infants and associated with an increased risk of mortality in toddlers aged 12–23 months at all seven study sites in Africa and South Asia (Kotloff et al., 2013). It is spread via the faecal-oral route including person-to-person, animal-to-person, waterborne and foodborne transmission (Fayer et al., 2000). *Cryptosporidium* is environmentally persistent with a low infectious dose (Fayer et al., 2000; Chappell et al., 2006). Disease incidence patterns show a distinct seasonality (Lal et al., 2012) and strong associations with weather globally (Jagai et al., 2009).

Most studies addressing the synergistic effects of environmental and social factors on cryptosporidiosis diarrhoea have been conducted in single small-scale sites. Conversely, global studies of cryptosporidiosis have focused on the relationship with climatic or social factors, with little empirical analyses of these determinants together. To our knowledge, there has been no global spatio-temporal analysis of the environmental and social factors that are associated with childhood cryptosporidiosis, despite recent evidence suggesting the burden in children is 2.5 times higher than previously estimated (Khalil et al., 2018).

The health impacts of extreme weather events are highly dependent on socio-economic development and availability of infrastructure such as access to sanitation and potable water (Fuller et al., 2015), as seen in Ecuador (Carlton et al., 2013), New Zealand (Britton et al., 2010) and Bangladesh (Hashizume et al., 2008), to name a few. Considerable variation in the magnitude of health responses to extreme weather events make it clear that a single-factor perspective for studying and managing waterborne disease risk is inadequate (Mellor et al., 2016). The lack of global analyses is an important gap in our understanding of how the spread of cryptosporidiosis in children may respond to future environmental and social change.

Through a systematic review of the published literature, we assess the available evidence regarding the effects of environmental and social conditions on diarrhoeal disease risk in children, demonstrated with cryptosporidiosis. We use the disease data from this review to develop mixed, spatio-temporal models that examine the effects of local weather and flooding history on disease risk, after controlling for publication bias, access to improved drinking water and sanitation, health resources and population density.

2. Methods

2.1. Systematic review of the literature

We systematically searched three electronic databases, PubMed, Web of Science and Embase to identify articles published from 1960 to 2014 using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1). The search strategy used the keywords "children" AND ("cryptosporidiosis" OR "cryptosporidium"). This initial review was completed by two authors independently (AL and EF), then, articles selected for inclusion based on title and abstract were sourced in full and reviewed again using the criteria described below. We excluded studies that had not been conducted continuously for a minimum of a full year to cover all seasons. Only studies where the primary outcome was a laboratory confirmed diagnosis of *Cryptosporidium* were included, as seasonal patterns for gastroenteritis can be pathogen specific. We also excluded studies where data was not reported temporally (monthly at a minimum), and by age group. No language or database restrictions were imposed on the searches. The reference lists of the full-text versions of the articles that fulfilled the eligibility criteria were manually searched to identify any further relevant manuscripts. Bibliographies of reviews published on *Cryptosporidium* epidemiology were also examined to identify additional sources for inclusion in the analysis.

Studies that satisfied the inclusion conditions but failed to be representative of the general population were excluded. These comprised studies that were (i) conducted in institutions (e.g. day-care centers), (ii) directed at specific ethnic groups and groups with certain characteristics (e.g. immune-compromised patients, travelers, refugees), (iii) studies focused solely on outbreaks as these studies can reflect disease patterns that may not be typical of disease patterns generally or clinically focused studies (e.g. drug efficacy studies or case reports). Animal and intervention studies were excluded. Fig. 1 demonstrates how the studies were classified and reasons for exclusion.

Data extraction from each eligible article was done independently by two investigators (EF and EW) and, in the case of discrepancies; the final decision was that of a third investigator (AL). From each eligible article, we recorded the authors and year of publication, location and study duration, study design, sample size and age range of study population. Table S2 in the electronic supplementary material provides details for the selected studies. Using the study sites' latitude and longitude each study site was plotted on a map using ESRI's ArcMap 10.3.1 software. Fig. 2 provides a map of study locations and the number of studies in each location. To map studies conducted across multiple cities, the capital city was used to visualize study location. To visualize the average incidence of cryptosporidiosis in children by hydrological subregions defined by the World Meteorological Organization (Fig. 1), each study was linked to the WMO subregion based on GIS layers provided by the Global Runoff Data Centre (2004). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Monthly data for each of the study months was extracted from the papers, either directly from the tables or extracted from graphs using DigitizeIt software (Bormann, 2012). From all eligible published studies, we extracted monthly data of laboratory confirmed cryptosporidiosis among children aged 0–15 years worldwide. Using each study site's longitude and latitude, we supplemented monthly illness data with time period specific precipitation, obtained from the KNMI Climate Explorer (http://climexp.knmi.nl/). Each study site was classified based on the Human Development Index (HDI) which was used as a summary measure of a country's development status, as published by the Human Development Report Office at the United Nations Development Programme (Jahan et al., 2015), and the country's population density, as published the United Nations Department of Economic and Social Affairs (2015). The HDI is a composite measure of the ability to acquire knowledge (measured by length of schooling), life expectancy at birth and gross national income per capita, to reflect more than just the economic status of a country (Jahan et al., 2015). The year of study was used to assign the HDI and population density. Based on the region and year, each study was assigned a value for total sanitation coverage as a percent of the total population. This data was extracted from the World Health Organization and United Nations International Children's

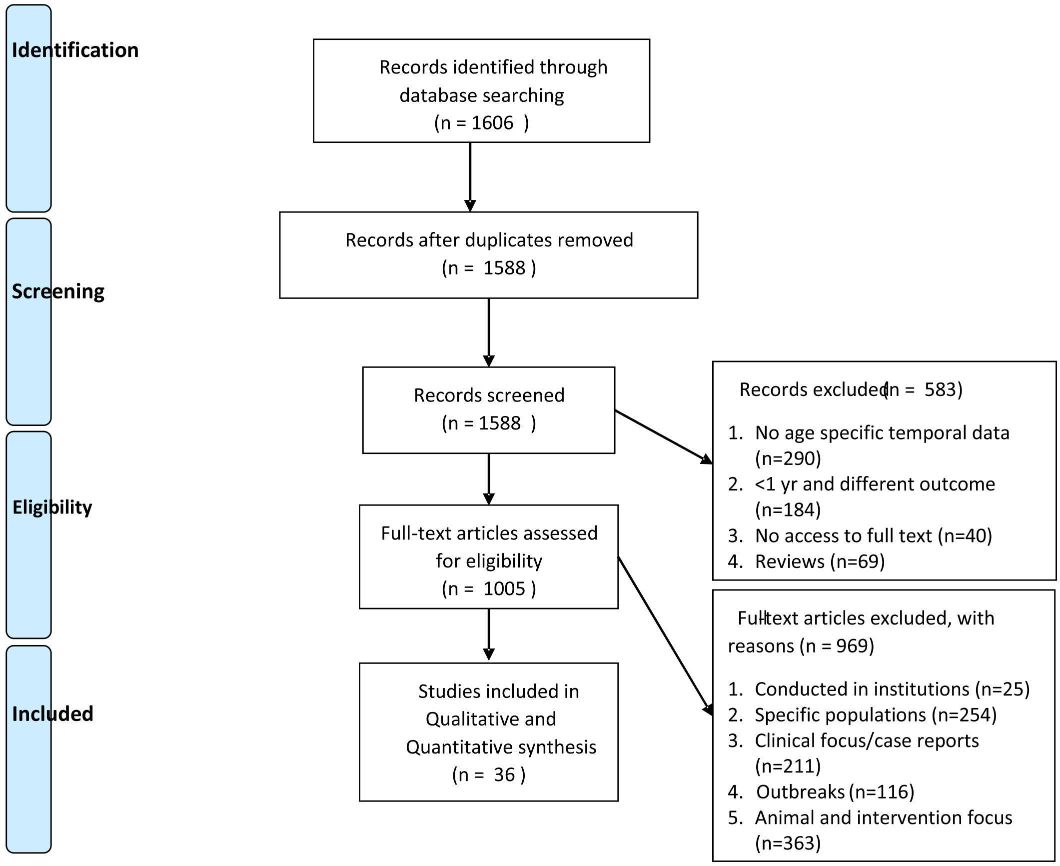

Fig. 1. PRISMA flowchart for selection of eligible studies.

Emergency Fund Joint Monitoring Programme for Water Supply and Sanitation (United Nations Environment Programme, 2017a). The number of deaths attributable to floods in the five years preceding the start of each study was used to measure flood risk. This data was obtained from the United Nations Environment Programme Environmental Data Explorer (United Nations Environment Programme, 2017b). Flooding history and the availability of sanitation infrastructure were categorized. For studies where between 0 and 500 people died in floods, the study was categorized as "low flood risk", 500–1000 people was considered "moderate risk", 1000–5000 people were categorized as "high risk" and areas where >5000 people perished in floods were categorized as "very high flood risk".

Assessment of study quality

Data quality for each eligible article was scored using a modified Newcastle–Ottawa checklist for bias assessment (Bawor et al., 2014). Bias was graded as high risk, moderate risk and low risk of

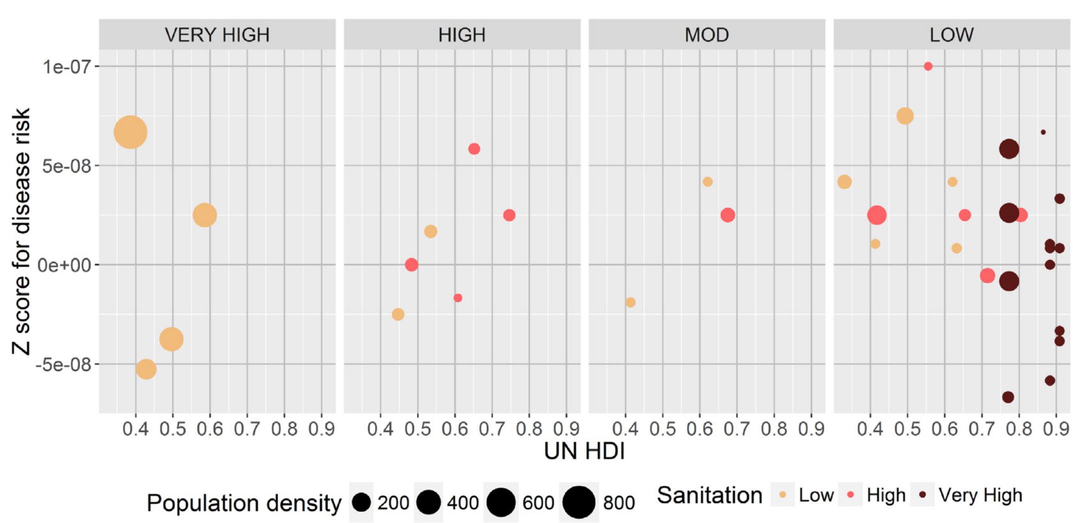

Fig. 2. Standardized cryptosporidiosis risk by flood risk category (very high, high, moderate, low), population density (size of circles) and availability of sanitation infrastructure (colors of circles) for each included study.

bias in the categories of selection bias (representative of the population of interest), performance bias (identification and adjustment for confounders), detection bias (using appropriate statistical methods for the outcome of interest) and information bias (clear methodology of outcome measurement and objective assessment of the outcome).

2.2. Assessment of publication bias

Using previously published methods, the reporting efforts for each region were calculated by estimating the frequency of infectious disease articles published each year from 1960 to 2014 (Yang et al., 2012; Jones et al., 2008). In PubMed, "infectious disease" and "region name" were used as keywords in the search of publications to generate an estimate of the reporting effort for each region. Reporting effort by geographic region was calculated as the total number of studies in each region divided by the total number of studies on infectious disease published over the entire time-period and multiplied by 100. To control for this spatial heterogeneity in reporting effort, the number of publications in each region (logged to the base 10) was used as a covariate in the spatio-temporal analysis (Yang et al., 2012; Jones et al., 2008).

2.3. Statistical analysis

We applied mixed effects spatio-temporal models to investigate the relationship between cryptosporidiosis incidence and the climatic variable (monthly average precipitation), while accounting for publication bias, population density, economic development (HDI) sanitation coverage and flooding history.

Data were delimited by latitude. Studies conducted between 0° and 20° on either side of the equator were categorized as "equatorial" (West Africa, Nigeria, the Gambia, Zambia, Brazil, Kenya, Costa Rica, Guatemala, Haiti), those between 20° and 35° were "tropical-subtropical" (West Mexico, Cuba, India, Bangladesh, Kuwait, South Africa, Tunisia, Western Australia) and those above 35° were "temperate" (United States, Ireland, England, West Scotland). To standardize the different outcome measures used in each study and the climatic variables, the raw values were standardized to have a mean of 0 and standard deviation of 1 prior to running the statistical analyses. Prior to analysis, collinearity among the variables was assessed using Pearson's correlation coefficient. Standardized cryptosporidiosis was not significantly associated with any of the covariates of interest ($r < 0.5$, $P > 0.05$) for any of the included studies. Significant correlations between the Human Development Index (HDI), latitude and population density were found although these correlations were all below $r = 0.5$. Population density and the number of publications for the region were log-transformed to the base 10 to aid in interpretation of model coefficients and normalize residuals (Dunn et al., 2010).

As the shape of the relationship between cryptosporidiosis and rainfall can vary in different climate zones, we examined the shape and included quadratic terms for monthly rainfall in the models for the tropical-subtropical (20°–35°) zone. Multiple comparisons using different lags for rainfall were run. As we were also interested in the interaction between rainfall and month the term "rainfall*month" was included in every model. All models were run using the "lme" package in the software R (R Development Core Team, 2012). Models were ranked using the Akaike Information Criterion (AIC), and models with the lowest AIC were chosen. The full models for each zone are provided in Table 1. To assess fit of the selected model, we saved model residuals and examined them against fitted values to assess model performance, through a Q-Q plot to detect obvious departures from model assumptions and a histogram of residuals to check for normality.

3. Results

3.1. Summary of effects of flooding history, population density, sanitation infrastructure and development on waterborne disease risk

Of the 1588 unique citations retrieved from the literature search, 36 studies were included from the 1009 full-text articles reviewed (Fig. 1). Study specific characteristics are shown in Table S2. Combined, the systematic search resulted in a total of 34 unique data sources in 22 countries, including southern and northern hemisphere temperate climates as well as tropical and arid regions of Asia, Oceania, Latin America and the Caribbean and Africa. Studies were published as early as 1982, with 42% (15/36) conducted in the 1980s, 30.5% (11/36) in the 1990s and 27.7% (10/36) in the 2000s. A large proportion of the published work is based on observational studies and analyses of data from retrospective surveillance systems (35 studies, 94.6%), fewer studies involve active recruitment and following of children (two studies, 5.4%). Of the 36 included studies, 11 were from Africa, seven from the United States, five from the Caribbean region, two from Kuwait, and one each from Australia, Bangladesh and Brazil.

The studies we reviewed used different measures of cryptosporidiosis. Of the 36 studies, 23 studies (63.8%) present outcome data as number of cases, seven studies (19.4%) present outcome as percent positive stools and six studies (16.6%) present outcome as prevalence.

Fig. 2 is an illustration of the standardized cryptosporidiosis risk as a function of the HDI for each flood risk category for each study. The sizes of the circles represent the population density with the colors showing the level of sanitation infrastructure (low <30%, high 40–80% and very high >80%). Areas classed as having very high flood risk (>5000 deaths due to floods in the five years preceding the study start date) are also areas with the highest population density and lowest availability of sanitation infrastructure and tend to be the least developed (extreme left of Fig. 2). All studies with very high sanitation infrastructure are based in areas with low flood risk (<500 deaths due to floods in the five years preceding the study start date) (extreme right of Fig. 2). This panel also has the highest number of studies, most of which have been conducted in high HDI areas. Areas with high (500–1000) and moderate (1000–5000) deaths due to floods in the five years preceding the study start date tend to be less developed with low to high availability of sanitation infrastructure.

3.2. Assessment of study quality

Bias assessment of included studies is as outlined in Table S1. There was moderate risk of selection bias in the majority of studies as many were convenience samples from diagnostic laboratories or selected health facilities; four were classified as low risk of bias with more representative population sampling outlined in study methods. Performance and detection bias was similarly moderate, where identification and assessment of potential confounders was limited and results often limited to descriptive frequency reporting only. Information bias was almost uniformly low, as laboratory methods to confirm the study outcome of cryptosporidiosis was clearly provided in all included studies, with the exception of two studies. The studies with moderate information bias risk included one that did not specify which laboratory method was used to identify *Cryptosporidium* oocysts (Baxby and Hart, 1986) and one study that was a case control study that did have an objective laboratory assessment of the cryptosporidiosis for cases, but not for the controls (Roy et al., 2004).

3.3. Assessment of publication bias

Fig. S1 shows a strong, temporal trend in the number of publications on infectious diseases from 1960 to 2014, which was closely correlated to the published incidence of cryptosporidiosis over time (Pearson correlation. 0.91). A similar temporal pattern was observed for all regions;

Table 1
Coefficients for chosen regression model for the Equatorial region, tropical-subtropical and temperate regions. Bold values indicate statistical significance at the 0.05 level. Reference categories include the month of April, Rainfall in April and low sanitation. NA = Categories not included.

	Equatorial region			Tropical-subtropical region			Temperate region		
	β	Low CI	High CI	β	Low CI	High CI	β	Low CI	High CI
Intercept	−0.01	−0.96	0.93	1.44	−1.39	4.27	−0.35	−1.15	0.44
Log population density	**0.46**	**0.10**	**0.81**	1.40	0.81	1.99	**0.33**	**0.02**	**0.64**
Number of publications	−0.06	−0.24	0.13	0.45	−0.36	1.26	−0.14	−0.43	0.14
UN HDI	−0.16	−0.96	0.63	−0.22	−1.11	0.68	−0.14	−0.87	0.59
Lag 1 month, rainfall (mm)	**0.49**	**0.04**	**0.93**	−0.11	−1.63	1.41	−0.67	−1.36	0.02
Lag 2 months, rainfall (mm)	0.17	−0.27	0.61	−1.07	0.13	1.33	−0.04	−0.72	0.64
Rainfall (mm)	0.31	−0.12	0.75	0.33	−0.82	1.47	0.01	−0.66	0.68
August	−0.14	−0.52	0.24	−0.03	−0.46	0.40	0.30	−0.11	0.72
December	0.07	−0.34	0.48	0.25	−0.18	0.68	−0.23	−0.67	0.21
February	−0.09	−0.46	0.28	0.02	−0.39	0.43	−0.12	−0.51	0.28
January	−0.17	−0.55	0.22	−0.40	−0.81	0.01	0.08	−0.32	0.48
July	0.31	−0.09	0.71	0.15	−0.27	0.58	0.42	−0.01	0.84
June	0.31	−0.07	0.68	0.13	−0.27	0.53	−0.13	−0.56	0.29
March	−0.07	−0.47	0.34	−0.12	−0.56	0.31	−0.03	−0.42	0.36
May	−0.15	−0.54	0.25	0.02	−0.43	0.46	0.08	−0.33	0.48
November	−0.03	−0.42	0.36	0.01	−0.40	0.41	−0.08	−0.51	0.35
October	0.14	−0.24	0.53	−0.28	−0.73	0.17	0.32	−0.10	0.74
September	−0.06	−0.49	0.37	0.28	−0.16	0.71	0.15	−0.31	0.61
Moderate sanitation	−0.22	−0.52	0.09	NA	NA	NA	0.01	−0.32	0.34
Good sanitation	NA	NA	NA	NA	NA	NA	−0.66	−2.14	0.83
Rainfall in August	0.07	−1.09	1.23	−0.23	−1.87	1.40	−1.23	−2.68	0.21
Rainfall in December	0.08	−0.92	1.09	**−2.33**	**−4.03**	**−0.63**	−0.92	−2.06	0.21
Rainfall in February	1.07	0.23	1.91	0.13	−1.17	1.42	−0.46	−1.65	0.73
Rainfall in January	0.73	−0.18	1.64	−0.73	−2.14	0.68	0.47	−0.62	1.57
Rainfall in July	−0.16	−1.47	1.16	−0.71	−2.25	0.84	−1.17	−2.93	0.58
Rainfall in June	0.13	−1.15	1.40	0.01	−1.46	1.49	0.81	−0.72	2.35
Rainfall in March	0.83	−0.10	1.75	0.64	−0.77	2.06	−0.49	−1.70	0.72
Rainfall in May	−0.07	−1.10	0.97	0.74	−0.86	2.34	0.10	−1.16	1.36
Rainfall in November	−0.71	−1.93	0.51	0.72	−0.69	2.13	0.71	−0.49	1.90
Rainfall in October	0.48	−1.09	2.05	−0.54	−2.27	1.19	1.81	0.33	3.29
Rainfall in September	−0.01	−0.23	0.22	−0.03	−0.26	0.20	−0.08	−0.31	0.15
Random effect									
Flooding history	**0.23**			0.31			4.65		

Africa (Pearson correlation with overall trends 0.97), Middle East (Pearson correlation with overall trends 0.96), Europe (Pearson correlation with overall trends 0.99), Latin America (Pearson correlation with overall trends 0.90), Asia (Pearson correlation with overall trends 0.98), Oceania (Pearson correlation with overall trends 0.70), North America (Pearson correlation with overall trends 0.97). Both the number of reported cryptosporidiosis cases and the number of publications for all infectious diseases increase through time (logged to the base 10) (Fig. S1). The majority of publications on infectious diseases were spatialized to Africa (39%), followed by Europe (27%), Asia (17%), North America, including Latin America (12%), Middle East (6%), and Oceania (0.3%).

3.4. Statistical analysis

Table 1 shows the coefficients for each of the fixed effects run for each zone delineated by latitude and the random effect for flooding history. In the equatorial zone (0°–20°), the most parsimonious full model (after testing a range of different lags for rainfall) had an AIC of 698.24. The goodness of fit Q-Q plot for the chosen model showed a slight lack of fit at the upper and lower quantiles (Fig. S2a), which could be “due to the inability of the model to account for some of the variation in the tails of the distribution of the residuals, rather than a misspecified functional form for the model” (Mantyka-pringle et al., 2012). The graph of the fitted values versus residuals showed no obvious pattern and the histogram of the residuals was not obviously skewed. Overall, the rainfall lagged by one month (Incidence Risk, (IR) 1.62, 95% Confidence Interval (CI) 1.04–2.54), logged population density (IR 1.57, 95%CI 1.10–2.25) and rainfall in February (compared to rainfall in April) (IR 2.91, 95%CI 1.25–6.74) were significantly positively associated with the published risk of cryptosporidiosis. The random effect of flooding history was 0.23 (95% CI 0.07–0.68) and the residual standard deviation was 0.81.

In the subtropical-tropical latitudes (20°–35°), the most parsimonious model had an AIC value of 654.90. The goodness of fit Q-Q plot for the chosen model showed a slight lack of fit at the upper quantile (Fig. S2b). The graph of the fitted values versus residuals showed no obvious pattern and the histogram of the residuals was not obviously skewed. Overall, logged population density (IR 1.39, 95%CI 1.01–1.90) and rainfall in October (compared to rainfall in April) (IR 6.10, 95%CI 1.02–26.84) were significantly positively associated with the published risk of cryptosporidiosis. The random effect of flooding history was 4.65 (95%CI 0.83–25.88) and the residual standard deviation was 0.84. A sensitivity analysis performed on studies from latitude 20°–29° showed no improvement in model performance and results were broadly consistent with those for the whole latitude band.

In the temperate zone, that is studies conducted over 35° latitude, the most parsimonious model had an AIC value of 631.49. The goodness of fit Q-Q plot for the chosen model showed a lack of fit at the upper quantile (Fig. S2c). The graph of the fitted values versus residuals showed no obvious pattern and the histogram of the residuals was not obviously skewed. Overall, logged population density (IR 4.06, 95%CI 2.25–7.32) was significantly positively associated with the published risk of cryptosporidiosis. Rainfall in December (compared to rainfall in April) (IR 0.09, 95%CI 0.01–0.53) and in January (compared to April) (IR 0.66, 95%CI 0.44–0.99) were significantly inversely associated with the published risk of cryptosporidiosis in children. The random effect of flooding history was 0.31 (95% CI 0.10–1.00) and the residual standard deviation was 0.84. For all models, the retention of flooding history as a random effect both improved model fit and addressed independence issues related to using multiple data points from each study (Kennedy and El-Sabaawi, 2017).

4. Discussion

Clear geographic patterns at a global scale are evident in the published incidence of waterborne disease, illustrated with cryptosporidiosis, the leading cause of parasitic diarrhoea among children. Globally, rainfall and population density were associated with childhood cryptosporidiosis. These results are broadly consistent with the known latitudinal gradient in human infectious disease distribution (Jones et al., 2013). Generally, the strength of the association with rainfall decreased at higher latitudes. The human development index was not associated with the reported incidence of cryptosporidiosis (Tables S2–S4), suggesting that local weather and demography may be more important than country specific development for childhood cryptosporidiosis. Flooding history was important in the equatorial region, as shown by the lower residual variance, providing a fundamental context to advocate for integrated flood risk and health outcome planning in regions that expect increased flooding.

The strengths of our analysis include a structured approach to selecting articles and integrating data from multiple fields, including meteorology, hydrology and observational epidemiology. Based on our results we now have a comprehensive overview on what is known about flooding history and waterborne transmission of cryptosporidiosis diarrhoea among children. Some of the generalizations from this study include the limited number of papers on cryptosporidiosis until the early 1990s; we have now systematically and quantitatively assessed the trajectory of this literature. A broad geographic range is represented in the disease incidence data, but there is a concentration of effort areas such as Africa. We acknowledge that this bias in the larger picture may be partly due to our search strategy. We limited our review to articles published in English or foreign language articles with abstracts in English which may have decreased our ability to collect the broadest sample of reports on these exposures. However, only 39 of the 1588 articles captured in our initial search (which was not restricted by language) were rejected based on language. Many of these reports were considered irrelevant because review of the titles and abstracts determined that they did not explore the relationship between cryptosporidiosis in children at the temporal scale needed.

Confounding presents a substantial challenge for assessments of the impacts of climate change on infectious disease (Ebi et al., 2013). Our study shows that populations at lower latitudes are much more likely to have high population densities and lower socio-economic development and therefore higher disease risk due to pathways other than environmental transmission, such as hygiene, water and sanitation infrastructure. Although we compiled data from a relatively large number of studies, our sample sizes were limited for combinations of drivers. The fact that for High HDI areas such as North America, there was a positive correlation between increasing population density and HDI with an inverse pattern seen in low and medium HDI areas suggests that differentiating the context-dependent effects of HDI, latitude and population density may be possible as more high-resolution data on specific drivers become available. Our analyses indicate that data on human population density and socio-economic development act as reasonable proxies for some of the anthropogenic changes that influence infectious disease incidence.

A related problem is the limited availability of pathogen specific data. Deficiencies in the current availability and quality of infectious disease data prevent comprehensive mapping for all but a few diseases (Hay et al., 2006, 2013). The generally moderate quality of the included studies (Table S1) limits detailed investigation. The Global Burden of Disease collaboration represents a significant step forward in the effort to provide comparable and considerable spatial and temporal coverage of human disease data. Our results support previous studies showing that climatic factors are important drivers of diarrhoea. The inclusion of flooding history in the current study is novel. With an understanding how historical weather extremes are related to child health, we may be able to better integrate climate change into flood management and human health prioritization decisions.

Implications for child health in a changing environment

Recent global reviews have shown a positive association of temperature and rainfall with all-cause diarrhoea (Carlton et al., 2015; Levy et al., 2016) and suggested a mechanistic systems based approach that involves environmental and engineered infrastructure to reduce the risk of diarrhoea in the context of climate change (Mellor et al., 2016). The need for greater integration between social and natural sciences to understand the region specific impacts of climate change on population health has also been emphasized (McMichael et al., 2015). In rural Nigeria, heavy rainfall has an important impact on child health, irrespective of the measure of child welfare used, with a significant and positive impact on the incidence of diarrhoea (Rabassa et al., 2014). In India, children exposed to drought around birth and in the first trimester of pregnancy (embryonic stage) were more likely to be underweight compared to children born in first and second quarters after a drought (Kumar et al., 2016). Despite this literature, there has been little multi-country investigation into how these factors shape childhood health. We agree with the Late Emeritus Professor Tony McMichael who observed that "Children warrant special concern, both as children per se and as the coming generation likely to face ever more extreme climate conditions later this century" (McMichael, 2014). There is also increasing evidence of the potential risks to water and sanitation services posed by climate change and the need to integrate measures of climate resilience into water safety plans (Howard et al., 2016). Our finding that local rainfall is a determinant of cryptosporidiosis in children globally, after accounting for publication bias and sanitation infrastructure provides a strong argument for an integrated and child-centered water protection policy, in the context of an increasingly variable climate.

Flooding can increase microbiological pollution of surface waters, with contamination due to *Cryptosporidium* spp. being 2.61 times higher during and after heavy rain (Young et al., 2015). To our knowledge, including flooding history as well as current rainfall as a determinant of childhood cryptosporidiosis at the global scale is novel. Our finding that historical flooding is an important determinant of reported disease in the equatorial region where the burden of cryptosporidiosis is currently the highest provides a timely opportunity for researchers to engage with environmental managers and industry to prevent microbiological water pollution.

5. Conclusions

Understanding the role of key environmental influences on childhood infections is an important aspect of both disease response and public health prevention strategies. Our findings add to the mounting evidence that environmental changes that include local weather and climate extremes in addition to increasing population density will create scientific challenges and community concerns for disease management.

Competing interests

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2019.02.365.

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